Office Action Summary	Application No.	Applicant(s)	
	10/802,516	LOH ET AL.	
	Examiner	Art Unit	
	PABLO WHALEY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10,11 and 13* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10 and 11* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-5, 10-11, and 13 are pending.

Claim 13 is withdrawn.

Claims 1-5 and 10-11 are rejected.

Claims 6-9 and 12 are cancelled.

Non-Elected Invention

Newly submitted claim 13 is directed to a method for the production of the fusion protein of claim 1. Applicant's election of the fusion protein of Group I (Claims 1-11) with traverse in the reply filed on 01/25/2006 is noted. Group I was directed to a method of identifying a sequence of a nucleic acid. Group II (Claim 13) is directed to a method for producing a fusion protein..

The inventions of Groups I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the method as claimed could be used to make many other species of fusion proteins with different sized inserts, for example. Similarly, the claimed fusion protein could be made by a different method that requires other types of media and has specific temperature and pH requirements. Thus, the search for the two groups together would present an undue search burden as they are directed to a fusion protein (i.e. product) and a method that are generally distinct and separate.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claim 13 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. For these reasons, Group I and Group II are not rejoined and the FINALITY of this requirement is still deemed proper.

Priority

This application has priority to US Provisional Application 60/456,965, filed 03/21/2003.

Withdrawn Rejections

The rejection of claims 1-6 and 8-11 under 35 U.S.C. 112, second paragraph, are withdrawn in view of applicant's amendments filed 3/21/2008.

The rejection of claims 1 and 2 under 35 U.S.C. 103(a) as being made obvious by Doi in view of Sevcik, Hochstrasser, and Varshavsky is withdrawn in view of applicant's arguments filed 11/06/2007.

The rejection of claims 1-5 under 35 U.S.C. 103(a) as being made obvious by Doi in view of Sevcik, Hochstrasser, Varshavsky, Pace, and Wintrode is withdrawn in view of applicant's arguments filed 11/06/2007.

The provisional rejection of claims 1-6 and 8-11 for obviousness-type double patenting as being unpatentable over claims 1-11 of co-pending Application No. 11/670,966 is withdrawn in view of the Terminal Disclaimer filed 03/21/2008.

Terminal Disclaimer

The terminal disclaimer filed on 03/21/2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Application 10/802,516 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Objections

Claim 3 is objected to because of the following informalities: Claim 3 is grammatically incorrect, and should recite "insert" instead of "iinsert." Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

This rejection is newly applied.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 requires a fusion protein wherein the insert protein and regulatory domain is ubiquitin, target protein and cytotoxic domain is barnase, the amino-carboxyl length is 38 angstrom, the initial amino acid surface loop comprises the position "Pro64", the terminal amino acid surface loop comprises the position "Thr70", and the alpha-carbon-alpha-carbon length is about 10.4 angstrom. However, it is unclear what these specific distances and positions are related to with regards to ubiquitin and barnase. A review of the specification shows that the ubiquitin molecule has loops and turns, and shows the N-C terminal length in the ubiquitin molecule that is about 38 angstroms in its folded conformation [p.15 and Fig. 2A], and that the barnase molecule has a surface loop in which the carbon-alpha-carbon-alpha length, measured from the Pro64 to the Thr70 position is about 10.4 angstroms [p.15, lines 15 to bottom, Fig. 2A, Fig. 2B]. However, this description lacks sufficient detail as to what these specific positions and distances represent with regards to the specific insert domain positions recited in the claimed invention.

Claim 11 recites "the controllable first and second effector signals" (lines 4-5). There is lack of antecedent basis for this limitation, as parent claim 10 does not recite controllable first and second effector signals. It is noted that dependent claim 3 does have antecedent basis for controllable effector signals.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

This rejection is newly applied.

Claims 1-5 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims, as currently written, are drawn to a fusion protein comprising a ubiquitin insert protein having an insert regulatory domain lying between an amino terminal and a carboxyl terminal of the ubiquitin insert protein; and, a barnase target protein having a surface loop that begins at an alpha carbon of an initial amino acid of the surface loop and terminates at an alpha carbon of a terminal amino acid of the surface loop, the surface loop comprising a cytotoxic target domain of the barnase target protein, wherein, the ubiquitin insert protein is inserted at a point within the surface loop between the alpha carbon of the initial amino acid of the surface loop and the alpha carbon of the terminal amino acid of the surface loop, such that an amino-carboxyl length of the ubiquitin insert protein is at least two-times greater than an alpha-carbon-alpha-carbon length of the barnase target protein.

In analysis of claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, regarding genus/species situations, the written description guidelines note that "satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register:

December 21, 1999 (Volume 64, Number 244), revised guidelines for written description, which can be obtained from the US PTO website: <http://www.uspto.gov>).

In the instant case, claim 1 requires a ubiquitin insert protein having an insert regulatory domain lying between an amino terminal and a carboxyl terminal of the ubiquitin insert protein; and, a barnase target protein having a surface loop that begins at an alpha carbon of an initial amino acid of the surface loop and terminates at an alpha carbon of a terminal amino acid of the surface loop, wherein, the ubiquitin insert protein is inserted at a point within the surface loop between the alpha carbon of the initial amino acid of the surface loop and the alpha carbon of the terminal amino acid of the surface loop. Ubiquitin is well conserved [NCBI, Conserved Domains search for "ubiquitin", p.1]The specification discloses an example wherein the ubiquitin molecule is inserted between amino acid residue 66 and 67 of barnase [p.15, lines 20 downward], however this limitation is not recited in claim 10. Therefore the written description of ubiquitin insert regulatory domain is not acceptable. Given that the genus for ubiquitin proteins essentially includes all ubiquitin genes of any length, and given that the claims are not limited to any specific region of the ubiquitin gene within the barnase target protein, it is unclear what domain of ubiquitin is actually inserted into the barnase target protein. The specification as filed does not provide a limiting definition for a ubiquitin insert protein and does not provide any SEQ ID numbers for the claimed ubiquitin insert protein. Therefore one of ordinary skill in the art would have reasonable doubt as to what length of ubiquitin insert protein is inserted into the barnase target protein at the time the application was filed. Additionally, one of ordinary skill in the art would have reasonable doubt as to what point within the surface loop of barnase the insertion of ubiquitin occurs such that the amino-carboxyl length of the ubiquitin insert protein is at least two-times greater than an alpha-carbon-alpha-carbon length of the barnase target protein at the time the application was filed.

Claim 1 is directed to a fusion protein comprising a ubiquitin insert protein and a barnase target protein. The specification discloses that the barnase target protein is produced exclusively by *Bacillus*

amyloliquefaciens [Specification, p.15], and has one catalyitic domain that is functionally cytotoxic to all mammalian cell types. Barnase is a member of the family of homologous microbial ribonucleases, and is well conserved [NCBI, Conserved Domains search for "barnase", p.1]. However, Pedersen et al. teaches that there is natural variability between ribonucleases that yields mutants with increased thermal stability [Abstract], and presents a listing of amino acid compositions deduced from barnase variants with varying levels of thermodynamic stability [Table 2 and p.121, Col. 1]. Given applicant's lack of disclosure for the different types of barnase variants and their functionality at different temperatures, one of ordinary skill in the art would have reasonable doubt that applicant's were actually in possession of a fusion protein with a barnase target domain that functioned for all barnase protein variants at the time the application was filed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Pablo S. Whaley/

Patent Examiner

Art Unit 1631

/John S. Brusca/
Primary Examiner, Art Unit 1631